REMARKS

Favorable reconsideration, entry of this Amendment, and allowance are respectfully requested. Claims 1, 5 to 16, and 21 are pending in this applications. Applicants have amended claim 1 and canceled claims 7 to 10 without prejudice to their right to pursue the canceled subject matter in a later filed divisional or continuation application. Support for the amendments to claim 1 can be found in the instant specification, *inter alia*, in claims 11 to 15; therefore, the amendments to claim 1 do not include new matter. Thus, upon entry of this Amendment claims 1, 5 to 6, 11 to 16 and 21 are pending and at issue.

I. RESPONSE TO REJECTION UNDER 35 U.S.C. U.S.C. §103(A)

In the December 31, 2003 Advisory Action, the Examiner maintained his rejection of the claims under 35 U.S.C. §103(a) as allegedly unpatentable over Kath et al. (U.S. Pat. No. 6,284,764 B1)(hereinafter "the '764 patent"). Applicants respectfully traverse the Examiner's rejection of the claims of the instant application under 35 U.S.C. §103(a), in view of the '764 patent for those reasons already of record, together with the following comments.

In the Advisory Action, the Examiner noted a perceived deficiency in Applicants' December 11, 2003 response to this basis of rejection as follows:

> The traverse of the 103(a) rejection is unpersuasive. It is agreed that the reference is available only under 102e. Applicants refer to MPEP 706.02k, but that deals with a provisional rejection over an application, not the circumstance here. Correct is 706.02(l), and specifically, 706.02(l)(2)(II), which states 'The common ownership must be shown to exist at the time the later invention was made. A statement of present common ownership is not sufficient.' Advisory Action at 2.

The Examiner noted that Applicants' statement of common ownership should be in accordance with that provided in MPEP 706(l)(2)(II). Accordingly, as provided in MPEP 706(l)(2)(II), *Applicants submit that the instant application and the '764 patent, were, at the time the later invention was made, owned by, or subject to an obligation of assignment to Pfizer Inc.* Therefore, the '764 patent does not qualify as prior art under 35 U.S.C. §103(a) due to the exemption provided for commonly owned prior art under 35 U.S.C. §102(e) in 35 U.S.C. §103(c). Accordingly, Applicants' respectfully request the Examiner to reconsider and withdraw the instant rejection under 35 U.S.C. §103(a).

II. REJECTION UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUS-TYPE DOUBLE PATENTING

On pages 2-3 of the Advisory Action, the Examiner maintained the obviousness-type double patenting rejection of the instant claims over claims 1-20 of the '764 patent.

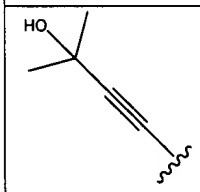
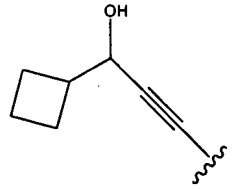
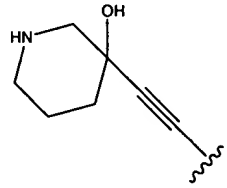
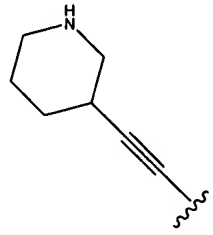
Without conceding the propriety of the rejection and purely in the interest of advancing prosecution on the merits, Applicants have amended claim 1 to delete reference to compounds in which R^4 comprises an alkene or alkyne linkage to a cyclic moiety, R^9. Similarly, Applicants have deleted claims 7 to 10. With respect to the subject matter deleted by this amendment, Applicants reserve the right to pursue the deleted subject matter in a subsequent continuation or divisional.

Further, submitted herewith is a copy of a publication, Bhattacharya et al., Biochem. Biophys. Res. Commun. (2003), 307: 267-73 ("Bhattacharya") which shows that the subgenus of quinazoline derivatives now claimed exhibit surprising and unexpected benefits when compared to the genus of quinazoline derivatives disclosed in the '764 patent. In particular, the Examiner's attention is directed to Table 1 of Bhattacharya and the accompanying discussion beginning on page 269 *et seq.* (beginning at the first full paragraph of the second column). Bhattacharya shows that derivatives of the 4-anilino group (the "head group") of the 6-alkynyl-4-anilinoquinazoline "with small, non-polar substituents at the aniline 3-position such as ethynyl (1), methyl (2) or bromo (3) all provide exceptional potency against EGFR kinase, but 80-100x less activity against erbB2 kinase." (Bhattacharya, 269). Moreover, Bhattacharya observed that the

> fact that selectivity of quinazoline based inhibitors within the erbB family of kinases can be altered by changes to the 4-anilino substituent is evidenced by compound **4** in which the small substituent at the aniline 3-position is removed and replaced with a large lipophilic phenyl ether at the aniline 4-position. This change effectively abolishes activity against EGFR while erbB2 inhibition is slightly enhanced. . . . Further refinement of the potency and selectivity profile of **4** was achieved by the incorporation of both a phenyl ether at the aniline 4-position and a small non-polar substituent such as methyl **5** or chloro **6** at the aniline 3-position. . . . [Further,] changing the terminal phenyl ether to a 3'-pyridyl ether provides additional improvement in erbB2 activity with a concomitant reduction in EGFR activity as observed in compounds **7** and **8**. (Bhattacharya, 269-70.)

Therefore, Bhattacharya shows that a systematic series of modifications to the head group of the quinazoline manifold can shift selectivity from 100-fold in favor of EGFR to greater than 100-fold in favor of erbB2.

Also submitted is a presentation by Kath et al., 226th ACS National Meeting, NY, NY, United States, September 7-11, 2003 ("Kath") which shows that in addition to the shift in selectivity that results from modifications to the head group, one also observes a further refinement in selectivity with modifications to the tail group of the quinazoline core (the "tail group" refers to the 6-position of the quinazoline). At slide 14, entitled "Potency/Selectivity of Alkyne Analogs", four different quinazolines are shown, each bearing the same head group. The tail groups and their respective activities are reproduced below:

Tail Group	erbB2 Kinase Activity	EGRF Kinase Activity
	670 nM	3.3 μM
	850 nM	3.0 μM
	405 nM	1.2 μM
	541 nM	771 nM

Therefore, seemingly minor modifications to the tail group can further refine the selectivity of the molecule for the erbB2 receptor vs. the EGFR receptor. This is also supported by the observations depicted in slide 18, entitled "SAR Translates to Different Tail

Groups" in which various modifications to the tail group yield compounds that exhibit from 14x selectivity to 57x selectivity for the erbB2 receptor. Slides 19-20 also confirm this observation.

Still further, slide 22, entitled "Changes to the Linker: CP-724714", shows that changing the linker of the tail group from an alkyne to an alkene or an alkyl group can also effect selectivity. In particular, each of the compounds depicted in slide 22 have the same head group, but each of the tail groups differ only in the linker between the quinazoline core and the amide. When the linker is an alkyl group the selectivity for the erbB2 kinase is 306 nM but when the linker is an alkyne the selectivity is 68 nM. Further refinements are observed when the linker changes from a cis-alkene (270nM) to a trans-alkene (8nM). Therefore, both Kath and Bhattacharya show that subtle changes to the tail and head groups of the quinazoline can markedly affect the selectivity of a compound for the erbB2 receptor.

Turning to the '764 patent and the instant claims, one can readily see that the head and tail groups disclosed in the '764 patent are quite varied, whereas the head and tail groups of the instant claims are more focused. In particular, the scope of the head groups disclosed in the '764 patent encompasses the full scope of compounds **1-8** of Bhattacharya, i.e., those having exceptional potency against EGFR kinase as well as compounds that are erbB2 selective. However, the compounds of the present invention have a more focused scope, e.g., the head groups of the instantly claimed compounds are akin to those of formula **7-8** of Bhattacharya which were found to have enhanced selectivity for erbB2. Still further, the scope of the tail groups of the compounds disclosed in the '764 patent encompasses a range of compounds far beyond that disclosed in either Kath or Bhattacharya, but as evidenced by the selectivity of the claimed compounds, narrowing the scope of the tail group to a specific subgenus such as those presently claimed results in a class of compounds with refined selectivity for the erbB2 receptor.

The instant specification states that the claimed compounds "are potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases, in particular *erbB2,* and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly in humans" (Specification at 24, lines 15-18). Therefore, Applicants submit that it was entirely surprising and unexpected that such subtle modifications to the structure of a small genus of compounds could affect the selectivity of those compounds so strikingly. Therefore, Applicants submit that the instantly claimed compounds are non-

obviate the enablement rejection.

CONCLUSION

In view of the foregoing remarks and attachments, Applicants submit that the claims are in condition for allowance and such action is earnestly solicited. If, after careful consideration of this Amendment, the Examiner maintains that there are issues which remain an impediment to allowance, he is invited to telephone the undersigned to discuss such matters in more detail.

Respectfully submitted,

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